UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/939,476	08/23/2001	Evan Y. Snyder	701039-051500-C	5389

7590 01/28/2003

NIXON PEABODY LLP
101 Federal Street
Boston, MA 02110

EXAMINER	
LOEB, BRONWEN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/939,476	SNYDER ET AL.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: information regarding Copy of Papers Originally Filed.

DETAILED ACTION

An amendment filed 19 February 2002 cancelled claims 1-15 and provided new claims 16-22.

Claims 16-22 are pending.

Specification

1. A preliminary amendment filed 23 August 2001 presented two amendments to the specification. These amendments were confusing for the following reasons: 1) There is no section titled "Background of the Invention" in the specification; and 2) there is already a priority claim on p. 1, lines 11-12. These amendments have been entered as follows: 1) "Cross Reference to Related Applications" was inserted in place of the phrase "Related Applications" on p. 1, line 9. 2) The second priority statement was inserted on p. 1, line 10. Thus this section of the specification will read:

> "This application is a Continuation of application 09/168,350 filed October 7, 1998, the disclosure of which is hereby incorporated by reference. This application is a continuation-in-part of pending U.S. Serial No. 09/133,873, filed August 14, 1998, which is incorporated herein by reference."

It is further noted that the USP number for 09/133,873 and the phrase "now abandoned" with respect to 09/168,350 have been amended into this section by informal Examiner's amendment.

Applicant is requested to acknowledge these amendments or to correct them in the response to this action.

2. The disclosure is objected to because of the following informalities: The page following page 12, which is presumed to be page 13, lacks a page number, the words on the bottom of the page are partially cut off and the bottom margin is less than ¾ of an inch (see 37 CFR 1.52(b)(i)). A replacement page is required.

Appropriate correction is required.

Claim Objections

3. Claim 21 is objected to because of the following informalities: The word "nontoxic" is misspelled as "no-toxic" on line 4 of claim 21. Claim 21 also lacks a step that clearly refers back to the preamble; amending the claim to recite "thereby providing treatment to a tumor present in the central nervous system" is suggested. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 16-22 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 16 encompasses treating *any* tumor mass in any living host subject by providing a genetically modified mammalian neural stem cell which expresses *any* exogenous protein product in-situ as a treatment. Claim 21 encompasses a method of treating any tumor present in the central nervous system of any host comprising administering murine neural stem cells capable of expressing cytosine deaminase.

The nature of the invention is a method of treating a tumor mass or a central nervous system tumor in a host using genetically modified neuronal stem cells. Delivery of a nucleic acid in vivo or ex vivo for therapeutic purposes constitutes gene therapy.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Palù et al, p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the

gene. While cell transplantation may overcome the obstacle of gene delivery, sustained expression of the gene remains problematic. See Verma et al, p. 240, third column, first paragraph and Palù et al, p. 10 "Gene therapy as viewed from the 21st century perspective". Specifically, the issue of efficiency of foreign gene expression in neural stem cells and what variables affect that expression is unknown. See p. 622, second column, first complete paragraph in Park et al (Gene Therapy (2002) 9:613-624). This reference, which includes two of the inventors as authors, also notes that "the field of NSC biology is at a very early state of development", that "many of our suggestions are higly speculative" and that "many important questions need to be addressed experimentally before using such cells in clinical applications" (p. 622, second column). It is noted that this reference was published several years *after* the earliest claimed priority date for the instant invention. Furthermore it is well known that success in murine models of glioma is *not* predictive of outcome in humans. See p. 370, first column, third complete paragraph in Noble (Nature Medicine (2000) 6:369-370). Noble also notes that the additional problem of turning off expression of a therapeutic agent has not be solved (p. 370, first column, second paragraph). While all of the references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Noble, p. 370, first column, lines 3-6.

The relative skill of those in the art of recombinant DNA techniques is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2): 1-3. More recently, two children treated with retroviral gene therapy for SCID have been diagnosed with leukemia, further indication of the unpredictable nature of gene therapy which persists to the current time. See Fox, Yahoo! News, January 14, 2003 (Accessed Jan. 14, 2003 from http://news.yahoo.com/news?tmpl=story2&cid=570&u=/nm/20030114/sc_nm/health_genetherapy_dc&printer=1). Furthermore, the skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. There is no direction provided as to how to overcome the obstacles to gene therapy recognized by leaders in the field, i.e. low efficiency of gene delivery and transient gene expression and gene expression which can be turned off at the appropriate time. Other than glioma, there is no teaching as to what specific tumors may be treated with the genetically modified neural stem cells or what specific therapeutic protein product should be expressed.

No working examples are disclosed which use a neuronal stem cell comprising a vector encoding a therapeutic agent to treat any tumor mass or CNS tumor.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine to what tumor types the genetically modified neural stem cells will migrate and collect, what therapeutic protein product to be expressed for what tumor type, what effect exogenous transgene expression would have in any neuronal stem cell type, whether the effect could be exploited for treatment of any tumor mass or CNS tumor, and how to get sufficient expression to induce at least some therapeutic effect and also be able to turn off expression when necessary. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed method of treating a brain tumor by providing a genetically modified neural stem cell comprising a vector encoding a a specific protein product.

Conclusion

Claims 16-22 are rejected.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 11:00 AM to 7:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

January 23, 2003

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600